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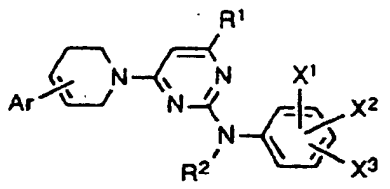
(54) 4-TETRAHYDROPYRIDYLPYRIMIDINE DERIVATIVES

(57) A 4-tetrahydropyridylpyrimidine derivative represented by formula (I):



(I)

wherein Ar represents a phenyl group substituted with 1 to 3 substituents selected from a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, and a trifluoromethyl group, a phenyl group, a thienyl group or a furanyl group; R^1 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an amino group or an amino group substituted with 1 or 2 alkyl groups having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, an alkenyl group having 2 to 5 carbon atoms or an alkynyl group having 2 to 5 carbon atoms; and X^1, X^2, and X^3, which may be the same or different, each represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5

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(Cont. next page)

Description

TECHNICAL FIELD:

[0001] This invention relates to a treating agent for diseases which corticotropin releasing factor (CRF) is considered to take part in, such as depression, anxiety, Alzheimer's disease, Parkinson's syndrome, Huntington's chorea, eating disorders, hypertension, digestive diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, head wounds, inflammation, and immunity-associated diseases.

BACKGROUND ART:

[0002] CRF is a hormone composed of 41 amino acids (see *Science*, vol. 213, pp. 1394-1397 (1981), *J. Neurosci.*, vol. 7, pp. 88-100 (1987)). It has been suggested that CRF plays a key role in biological reactions to stress (see *Cell. Mol. Neurobiol.*, vol. 14, pp. 579-588 (1994), *Endocrinol.*, vol. 132, pp. 723-728 (1994), and *Neuroendocrinol.*, vol. 61, pp. 445-452 (1995)). CRF functions through two routes; a route through the hypothalamo-hypophysial-adrenal system for acting on the peripheral immune system and the sympathetic nervous system, and a route through the central nervous system in which it functions as a neurotransmitter (see *Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, pp. 29-52 (1990)). CRF intracerebroventicularly administered to hypophysectomized rats and normal rats induces anxiety-like symptoms in both rats (see *Pharmacol. Rev.*, vol. 43, pp. 425-473 (1991) and *Brain Res. Rev.*, vol. 15, pp. 71-100 (1990)). That is, CRF is believed to participate in the hypothalamo-hypophysial-adrenal system and to function as a neurotransmitter in the CNS.

[0003] As Owens and Nemeroff collected in *Pharmacol. Rev.*, vol. 43, pp. 425-474 (1991), diseases in which CRF takes part include depression, anxiety, Alzheimer's disease, Parkinson's syndrome, Huntington's chorea, eating disorders, hypertension, digestive diseases, drug dependence, inflammation, and immunity-associated diseases. It has recently been reported that CRF is also involved in epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, and head wounds (see *Brain Res.*, vol. 545, pp. 339-342 (1991), *Ann. Neurol.*, vol. 31, pp. 48-498 (1992), *Dev. Brain Res.*, vol. 91, pp. 245-251 (1996), and *Brain Res.*, vol. 744, pp. 166-170 (1997)). Therefore, an antagonist against a CRF receptor is useful as a treating agent for these diseases.

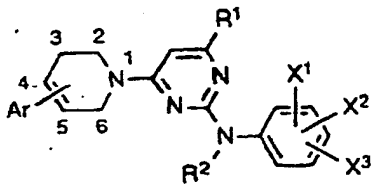
[0004] An object of the invention is to provide a CRF receptor antagonist effective as a treating agent or a prophylactic agent for diseases in which CRF is said to participate, such as depression, anxiety, Alzheimer's disease, Parkinson's syndrome, Huntington's chorea, eating disorders, hypertension, digestive diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, head wounds, inflammation, and immunity-associated diseases.

DISCLOSURE OF THE INVENTION:

[0005] As a result of extensive study on 4-tetrahydropyridylpyrimidine derivatives, the inventors have found that 4-tetrahydropyridylpyrimidine derivatives exhibits high affinity to a CRF receptor, thus completing the present invention.

[0006] The invention will be described hereinafter.

[0007] The invention relates to a 4-tetrahydropyridylpyrimidine derivative represented by formula (I):



(I)

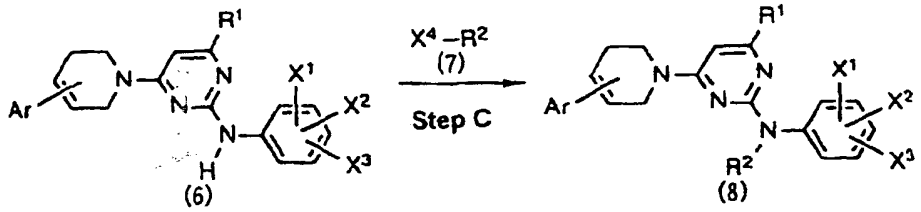
wherein Ar represents a phenyl group substituted with 1 to 3 substituents selected from a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, and a trifluoromethyl group, a phenyl group, a thienyl group or a furanyl group; R^1 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an amino group or an amino group substituted with 1 or 2 alkyl groups having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, an alkenyl group having 2 to 5 carbon atoms or an alkynyl group having 2 to 5 carbon atoms; and X^1, X^2, and X^3, which may be the same or different, each represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkylthio group having 1 to 5 carbon atoms, an amino group or an amino group substituted with 1 or

Step A:

[0012] A 1,2,3,6-tetrahydropyridine compound (1) and a 2,4-dichloropyrimidine compound (2) are allowed to react in an inert solvent in the presence of a base to form a compound of formula (3). Useful bases include amines, such as triethylamine, diisopropylethylamine, and pyridine; inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, and sodium hydride; alcoholates, such as sodium methoxide, sodium ethoxide, and potassium t-butoxide; and metal amides, such as sodium amide and lithium diisopropylamide. Useful inert solvents include alcohols, such as methanol, ethanol, isopropyl alcohol, and ethylene glycol; ethers, such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane; hydrocarbons, such as benzene and toluene; amides, such as N,N-dimethylformamide; acetonitrile, water; and mixtures thereof.

Step B:

[0013] The compound of formula (3) reacts with an aniline compound (4) in an inert solvent in the presence or absence of a base to give a compound (5) of the invention. Useful bases include amines, such as triethylamine, diisopropylethylamine, and pyridine; inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, and sodium hydride; alcoholates, such as sodium methoxide, sodium ethoxide, and potassium t-butoxide; and metal amides, such as sodium amide and lithium diisopropylamide. Useful inert solvents include alcohols, such as methanol, ethanol, isopropyl alcohol, and ethylene glycol; ethers, such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane; hydrocarbons, such as benzene, toluene, and xylene; amides, such as N,N-dimethylformamide; and dimethyl sulfoxide.



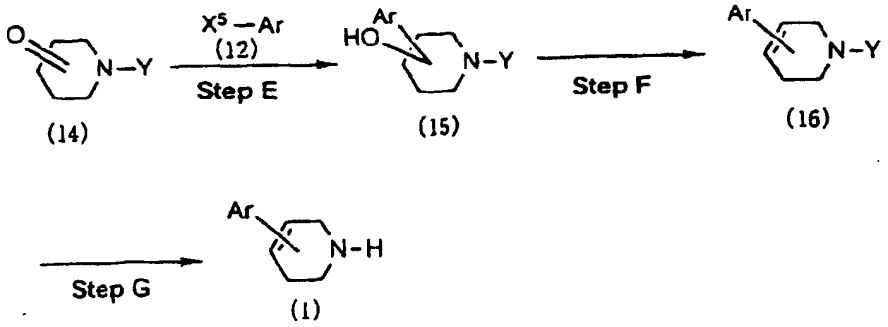
Step C:

[0014] A compound (6), which is the compound (5) wherein R^3 is a hydrogen atom, is led to a compound (8) of the invention by reaction with a halide (7) in an inert solvent in the presence of a base. Useful bases include amines, such as triethylamine, diisopropylethylamine, and pyridine; inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, and sodium hydride; alcoholates, such as sodium methoxide, sodium ethoxide, and potassium t-butoxide; and metal amides, such as sodium amide and lithium diisopropylamide. Useful inert solvents include alcohols, such as methanol, ethanol, isopropyl alcohol, and ethylene glycol; ethers, such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane; hydrocarbons, such as benzene, toluene, and xylene; amides, such as N,N-dimethylformamide; dimethyl sulfoxide, acetonitrile, water; and mixtures thereof.

Step F:

[0018] The alcohol compound (13) is led to a compound (8) of the invention by dehydration under an acidic condition or by conversion to an active species which is then subjected to reaction under a basic condition. The dehydration under an acidic condition is carried out in an inert solvent, such as an alcohol, e.g., methanol, ethanol, isopropyl alcohol or ethylene glycol; an ether, e.g., diethyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; a ketone, e.g., acetone or methyl ethyl ketone; water; or a mixed solvent thereof, using an acid, such as an inorganic acid, e.g., hydrochloric acid, hydrobromic acid or sulfuric acid; a hydrogen halide, such as hydrogen chloride or hydrogen bromide; or an organic acid, such as p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid or formic acid. The term "active species" means the alcohol compound (13) with its hydroxyl group sulfonylated or acylated or the alcohol compound (13) with its hydroxyl group substituted with a halogen atom. Such an active species is obtained by allowing the alcohol compound (13) to react with a sulfonyl chloride (e.g., methanesulfonyl chloride or p-toluenesulfonyl chloride), an organic carbonyl chloride (e.g., acetyl chloride), an organic carboxylic acid anhydride (e.g., acetic anhydride or trifluoroacetic anhydride), a halogenating agent (e.g., sulfonyl chloride or phosphoryl chloride), and the like in an inert solvent in the presence of a base. Useful inert solvents include ethers, such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane; hydrocarbons, such as benzene, toluene, and xylene; halides, such as chloroform and dichloromethane; and amides, such as N,N-dimethylformamide. Useful bases include amines, such as triethylamine, diisopropylethylamine, pyridine, and 4-dimethylaminopyridine; inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, and sodium hydride; and metal amides, such as sodium amide and lithium diisopropylamide. The reaction under a basic condition is a reaction between the active species of the alcohol compound (13) and a base in an inert solvent. Useful inert solvents include ethers, such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane; hydrocarbons, such as benzene, toluene, and xylene; halides, such as chloroform and dichloromethane; and amides, such as N,N-dimethylformamide. Useful bases include amines, such as triethylamine, diisopropylethylamine, pyridine, and 1,8-diazabicyclo[5.4.0]-7-undecene; inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, and sodium hydride; metal amides, such as sodium amide and lithium diisopropylamide; and alcoholates, such as potassium t-butoxide.

[0019] The compound of formula (1) used in process 1 is known *per se* or can be prepared from a ketone compound of formula (14) as follows.



[0020] Where the protective group Y of the ketone compound (14) is an alkoxycarbonyl group, an acyl group or a sulfonyl group, the compound (14) is led to a compound of formula (16) under the same conditions as in steps E and F. That is, the compound of formula (14) reacts with a metal compound, which is obtained from the compound of formula (12) and a metal reagent, to give an alcohol compound (15), which is then treated with an acid, such as an inorganic acid, e.g., hydrochloric acid, hydrobromic acid or sulfuric acid, an organic acid, e.g., trifluoroacetic acid, formic acid or methanesulfonic acid, a dioxane or ethyl acetate solution of hydrogen chloride, etc. In this case, dehydration and removal of the protective group are carried out simultaneously or stepwise to obtain the compound of formula (16) in which Y is a hydrogen atom, i.e., the compound of formula (1). In case only a dehydration reaction precedes, removal of the protective group Y can be achieved even with an inorganic base, such as sodium hydroxide, potassium hydroxide or barium hydroxide, to give the compound of formula (16) in which Y is a hydrogen atom. Where the alcohol of formula (15) is converted to its active species in the same manner as in step F followed by dehydration, the protective group is removed by the above-described acid or base treatment.

EXAMPLE 2

Synthesis of 2-[N-(2,4-dimethoxyphenyl)-N-ethylamino]-4-[4-(3,4-dichlorophenyl-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine:

[0027] 4-[4-(3,4-Dichlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-2-chloro-6-methylpyrimidine (500 mg), which was obtained from 2,4-dichloro-6-methylpyrimidine and 4-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyridine in the same manner as in Example 1, and 281 mg of N-ethyl-2,4-dimethoxyaniline were heated in 2 ml of ethylene glycol at 170°C for 1.5 hours. The reaction solution was poured into a saturated aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate. The extract was washed successively with water and a saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. The desiccant was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=4/1) and recrystallized from diethyl ether to give 360 mg of 2-[N-(2,4-dimethoxyphenyl)-N-ethylamino]-4-[4-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine.

[0028] The structure and physical properties data of the resulting compound and other compounds obtained similarly are shown in Table 1.

EXAMPLE 3

Synthesis of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-4-[4-(3-chlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine hydrochloride:

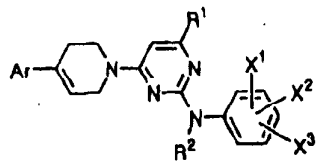
[0029]

(1) 2-[N-(2-Bromo-4-isopropylphenyl)-N-ethylamino]-4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-6-methylpyrimidine (14.25 g), which was obtained from 2,4-dichloro-6-methylpyrimidine and 4-(1,3-dioxolan-2-yl)piperidine in the same manner as in Example 1, was dissolved in 75 ml of tetrahydrofuran, and 75 ml of 4N hydrochloric acid was added thereto, followed by stirring at room temperature for 6 hours. The reaction solution was concentrated under reduced pressure to about 80 ml. The concentrate was poured into a saturated aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The desiccant was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=7/1 to 6/1) to give 12.93 g of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-6-methyl-4-(4-oxopiperidin-1-yl)pyrimidine as an oily substance.

(2) 3-Bromochlorobenzene (427 mg), 27 mg of magnesium, and a trace amount of iodine were heated in 5 ml of tetrahydrofuran under reflux for 1 hour. The reaction mixture was cooled with ice and added dropwise to a solution of 321 mg of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-6-methyl-4-(4-oxopiperidin-1-yl)pyrimidine in 3 ml of tetrahydrofuran, followed by stirring under ice-cooling for 1 hour and then at room temperature for an addition 1 hour period. The reaction mixture was again cooled with ice, and a saturated ammonium chloride aqueous solution was added thereto dropwise. After stirring at room temperature for 10 minutes, the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated ammonium chloride aqueous solution, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. The desiccant was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=4/1) to give 238 mg of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-4-[4-(3-chlorophenyl)-4-hydroxypiperidin-1-yl]-6-methylpyrimidine.

(3) To 170 mg of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-4-[4-(3-chlorophenyl)-4-hydroxypiperidin-1-yl]-6-methylpyrimidine was added 1.25 ml of trifluoroacetic acid, followed by stirring at room temperature for 2 days. The reaction solution was concentrated under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue. The mixture was extracted with ethyl acetate, and the extract was washed successively with a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. The desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=7/1). The resulting free amine was converted to its hydrochloride by treating with 4N HCl/ethyl acetate in methanol, and recrystallized from isopropyl alcohol-diisopropyl ether to give 131 mg of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-4-[4-(3-chlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine hydrochloride.

TABLE 1



Comp. No.[1]	Exp. No.[2]	Ar	X^1	X^2	X^3	R^1	R^2	Salt	m.p. (Recry. Sol.[3]) (°C)
1-01	1	Ph	2-Br	4-i-Pr	H	Me	Et	HCl	123.5-126.5 (Et_2O[4])
1-02	1	3-F-Ph	2-Br	4-i-Pr	H	Me	Et	HCl	117.5-120.0 (AcOEt[4])
1-03	1	3-F-Ph	2-Br	4-i-Pr	H	Me	$CH{\equiv}C\text{-}CH_2$	HCl	118.5-123.5 (AcOEt/IPE[4])
1-04	1	3-F-Ph	2-Br	4-t-Bu	H	Me	Et	HCl	137.0-142.0 (IPA/IPE)
1-05	1	3-F-Ph	2-I	4-i-Pr	H	Me	Et	H_2SO_4	248.0-249.0 (EtOH)
1-06	1	3-F-Ph	2-MeS	4-i-Pr	H	Me	Et	HCl	125.0-128.0 (IPA/IPE)
1-07	2	3-F-Ph	2-MeS	4-i-Pr	H	Me	c-$PrCH_2$	HCl	164.0-174.0 (AcOEt)
1-08	1	3-F-Ph	2-MeS	4-i-Pr	H	Me	$CH{\equiv}C\text{-}CH_2$	HCl	92.0-95.0 (AcOEt/Et_2O[4])
1-09	1	3-F-Ph	2-MeS	4-t-Bu	H	Me	Et	HCl	144.0-148.0 (AcOEt)
1-10	1	3-F-Ph	2-EtS	4-i-Pr	H	Me	Et	HCl	138.0-140.5 (AcOEt[4])
1-11	1	3-F-Ph	2-i-PrS	4-i-Pr	H	Me	Et	HCl	112.0-117.0 (AcOEt/Et_2O[4])
1-12	1	3-F-Ph	2-Br	4-Me_2N	H	Me	Et	HCl	116.0-119.0 (AcOEt[4])
1-13	2	3-F-Ph	2-MeO	4-MeO	H	Me	Et	-	127.0-129.0 (Et_2O)
1-14	2	3-F-Ph	2-Me	4-Me	6-Me	Me	Et	HCl	126.5-129.0 (AcOEt/IPE[4])
1-15	3	4-F-Ph	2-Br	4-i-Pr	H	Me	Et	HCl	183.0-185.0 (IPA/IPE)
1-16	1	4-F-Ph	2-MeS	4-i-Pr	H	Me	Et	HCl	136.0-139.0 (IPA/IPE)
1-17	1	4-F-Ph	2-Br	4-Me_2N	H	Me	Et	HCl	121.5-124.0 (IPA/IPE)
1-18	2	4-F-Ph	2-MeO	4-MeO	H	Me	Et	-	181.5-182.5 (AcOEt)

/To be cont'd.

TABLE 1 (cont(d.)

Comp. No.*	Exp. No.*2	Ar	X^1	X^2	X^3	R^1	R^2	Salt	m.p. (Recry. Sol.*3) (°C)
I-39	2	3-Cl-Ph	2-Me	4-Me	6-Me	Me	Et	HCl	120.0-122.5 (IPA/IPE)
I-40	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	Me	HCl	106.0-109.0 (AcOEt*4)
I-41	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	Et	-	91.0-92.0 (Hex)
I-42	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	n-Pr	HCl	137.0-140.0 (AcOEt*4)
I-43	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	n-Pen	HCl	118.0-120.5 (AcOEt*4)
I-44	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	i-Bu	HCl	124.0-127.0 (AcOEt*4)
I-45	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	CH_2=CH-CH_2	HCl	109.0-112.0 (AcOEt*4)
I-46	1	4-Cl-Ph	2-Br	4-i-Pr	H	Me	CH≡C-CH_2	HCl	120.5-123.0 (AcOEt*4)
I-47	1	4-Cl-Ph	2-Br	4-i-Pr	H	H	Et	-	amorphous*7
I-48	1	4-Cl-Ph	2-Br	4-c-Pen	H	Me	Et	HCl	133.0-138.0 (EtOH/IPE)
I-49	1	4-Cl-Ph	2-Br	4-i-Pr	H	i-Pr	Et	-	amorphous*8
I-50	1	4-Cl-Ph	2-MeS	4-n-Pr	H	Me	Et	HCl	125.0-128.5 (AcOEt*4)
I-51	1	4-Cl-Ph	2-MeS	4-i-Pr	H	Me	Et	HCl	134.5-135.0 (AcOEt*4)
I-52	1	4-Cl-Ph	2-MeS	4-i-Pr	H	Me	CH≡C-CH_2	HCl	111.0-115.5 (AcOEt/Et_2O*4)
I-53	1	4-Cl-Ph	2-MeS	4-n-Bu	H	Me	Et	HCl	120.0-123.0 (AcOEt*4)
I-54	2	4-Cl-Ph	2-MeS	4-c-Pen	H	Me	Et	HCl	131.5-136.5 (EtOH/IPE)
I-55	1	4-Cl-Ph	2-Br	4-Me_2O	H	Me	Et	HCl	115.5-118.5 (IPA/IPE)
I-56	1	4-Cl-Ph	2-Cl	4-Cl	H	Me	Et	HCl	112.0-114.0 (IPA/IPE)
I-57	1	4-Cl-Ph	2-Br	4-Br	H	Me	Et	HCl	111.0-114.0 (IPA/IPE)
I-58	2	4-Cl-Ph	2-MeO	4-MeO	H	Me	Et	-	159.0-159.5 (Et_2O)
I-59	2	4-Cl-Ph	2-Me	4-Me	6-Me	Me	Et	HCl	125.0-127.0 (IPA/IPE)

/To be cont'd.

Note:

*1: Compound No.

*2: Example No. used for synthesis

*3: Recrystallizing solvent;

Et_2O: diethyl ether

IPA: isopropyl alcohol

IPE: diisopropyl ether

AcOEt: ethyl acetate

Hex: hexane

*4: Crystallizing solvent

*5: NMR ($CDCl_3$) δ (ppm): 1.20 (t, J=7.1Hz), 2.22 (3H, s), 2.40-2.61 (2H, m), 2.98 (6H, s), 3.52-4.28 (6H, m), 5.79 (1H, s), 6.10 (1H, s), 6.68 (1H, dd, J=8.8, 2.9Hz), 6.99 (1H, d, J=2.9Hz), 7.10 (1H, d, J=8.8Hz), 7.19-7.42 (4H, m)

EIMS m/e: 525 (M^+), 446 (100%)

6 NMR ($CDCl_3$) δ (ppm): 1.00-1.67 (9H, m), 1.80-3.00 (8H, m), 3.00-4.40 (10H, m), 5.75-8.10 (9H, m)

EIMS m/e: 489 (M^+, 100%)

*7: NMR ($CDCl_3$) δ (ppm): 1.18-1.33 (3H, m), 1.27 (6H, d, J=6.8Hz), 2.45-2.63 (2H, m), 2.91 (1H, sept, J=7.0Hz), 3.50-4.30 (6H, m), 5.92 (1H, d, J=6.0Hz), 6.04-6.16 (1H, m), 7.14-7.26 (2H, m), 7.31 (4H, s), 7.50-7.56 (1H, m), 7.96 (1H, d, J=6.0Hz)

FABMS m/e: 511 (MH^+, 100%)

*8: NMR ($CDCl_3$) δ (ppm): 1.17 (6H, br d, J=6.6Hz), 1.24 (3H, t, J=7.0), 1.28 (6H, d, J=7.0Hz), 2.40-2.75 (3H, m), 2.92 (1H,

dichloro-6-methylpyrimidine were added thereto, and the mixture was stirred overnight under cooling with ice. The reaction solution was poured into a saturated aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate. The extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. The desiccant was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=3/1) to give 2.17 mg of 4-(5-phenyl-1,2,3,6-tetrahydropyridin-1-yl)-2-chloro-6-methylpyrimidine as crystals.

(3) 4-(5-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)-2-chloro-6-methylpyrimidine (1.10 g), 2-bromo-4-isopropylaniline hydrochloride (0.97 g), and diisopropylethylamine (0.50 g) were heated at reflux in 5 ml of ethylene glycol for 1 hour. The reaction solution was poured into a saturated sodium hydrogencarbonate aqueous solution and extracted with ethyl acetate. The extract was washed with water and then with a saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=3/1) to give 1.32 g of 2-[N-(2-bromo-4-isopropylphenyl)amino]-4-(5-phenyl-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine as an amorphous substance.

(4) In 12 ml of N,N-dimethylformamide was dissolved 1.21 g of 2-[N-(2-bromo-4-isopropylphenyl)amino]-4-(5-phenyl-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine, and 136 mg of a 60% oil dispersion of sodium hydride was added to the solution, followed by stirring at room temperature for 1 hour. To the mixture was added 570 mg of ethyl iodide, and the mixture was stirred at room temperature overnight. The reaction solution was poured into water and extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. The desiccant was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/acetone=9/1). The resulting free amine was converted to its hydrochloride by treatment with 4N HCl/ethyl acetate in methanol, and crystallized from ether to give 1.02 g of 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-4-(5-phenyl-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine hydrochloride.

[0036] The structure and physical properties data of the resulting compound and other compounds obtained similarly are shown in Table 2.

EXAMPLE 7

Synthesis of 2-[N-(4-isopropyl-2-methylthiophenyl)-N-ethylamino]-4-[5-(2-methylphenyl)-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine hydrochloride:

[0037] 4-[5-(2-Methylphenyl)-1,2,3,6-tetrahydropyridin-1-yl]-2-chloro-6-methylpyrimidine (905 mg), which was obtained from N-t-butoxycarbonyl-3-oxopiperidine, 2-methylphenylmagnesium bromide, and 2,4-dichloro-6-methylpyrimidine in the same manner as in Example 6, and 632 mg of N-ethyl-4-isopropyl-2-methylthioaniline were heated in 10 ml of ethylene glycol at 170°C for 1.5 hours. The reaction solution was poured into a saturated sodium hydrogencarbonate aqueous solution and extracted with chloroform. The extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. The desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate=10/1 to 4/1). The resulting free amine was converted to its hydrochloride by treatment with 4N HCl/ethyl acetate in dichloromethane and recrystallized from ethyl acetate/diethyl ether to give 1.05 g of 2-[N-(4-isopropyl-2-methylthiophenyl)-N-ethylamino]-4-[5-(2-methylphenyl)-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine hydrochloride.

[0038] The structure and physical properties data of the resulting compound and other compounds obtained similarly are shown in Table 2.

Note:

*1: Compound No.

*2: Example No. used for synthesis

*3: Recrystallizing solvent;

Et_2O: diethyl ether

IPA: isopropyl alcohol

IPE: diisopropyl ether

AcOEt: ethyl acetate

Hex: hexane

*4: Crystallizing solvent

*5: NMR ($CDCl_3$) δ (ppm): 1.21 (3H, t, J=7.1Hz), 1.26 (6H, d, J=6.9Hz), 2.13-2.37 (5H, m), 2.91 (1H, sept, J=6.8Hz), 3.40-4.28 (6H, m), 5.85 (1H, m), 6.14 (1H, s), 7.10-7.35 (6H, m), 7.48 (1H, s)

SIMS m/e: 525 (MH^+)

TEST EXAMPLE

CRF receptor Binding Assay

[0039] The frontal cortical membranes of rats were used as a membrane preparation. [^{125}I]-CRF was used as a [^{125}I]-labeled ligand.

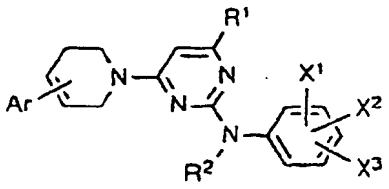
[0040] A binding reaction using a ^{125}I-labeled ligand was carried out in accordance with the following method described in *The Journal of Neuroscience*, vol. 7, p. 88 (1987).

Membrane preparation:

[0041] The rat frontal cortex was homogenized in a 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$ and 2 mM EDTA, and centrifuged at 48,000 x g. The pellet was washed with a Tris-HCl buffer. The pellet was suspended in a 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA, 0.1% bovine serum albumin and 100 kallikrein units/ml-Aprotinin to prepare a membrane preparation. CRF receptor binding assay:

[0042] The membrane preparation (0.3 mg-protein/ml), ^{125}I-CRF (0.2 nM), and a test compound were allowed to react at 25°C for 2 hours. After completion of the reaction, the reaction mixture was filtered by suction through a glass filter (GF/C) having been treated with 0.3% polyethyleneimine. The glass filter was washed three times with a phosphate-buffered saline solution containing 0.01% Triton X-100, and then the radioactivity of the filter was measured in a gamma counter.

[0043] The binding in the presence of 1 μM CRF was taken as a nonspecific binding of ^{125}I-CRF, and the difference between the total binding and the nonspecific binding was taken as specific binding. ^{125}I-CRF in a given concentration (0.2 nM) and a test compound in a varied concentration were allowed to react under the above-described conditions to



(I)

wherein Ar represents a phenyl group substituted with 1 to 3 substituents selected from a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, and a trifluoromethyl group, a phenyl group, a thienyl group or a furanyl group; R^1 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an amino group or an amino group substituted with 1 or 2 alkyl groups having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, an alkenyl group having 2 to 5 carbon atoms or an alkynyl group having 2 to 5 carbon atoms; and X^1, X^2, and X^3, which may be the same or different, each represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkylthio group having 1 to 5 carbon atoms, an amino group or an amino group substituted with 1 or 2 alkyl groups having 1 to 5 carbon atoms, or a pharmaceutically acceptable salt thereof.

2. A 4-tetrahydropyridylpyrimidine derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein, in formula (I), Ar is at the 4-position of the tetrahydropyridine ring and is a phenyl group substituted with 1 to 3 substituents selected from a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, and a trifluoromethyl group, a phenyl group, a thienyl group or a furanyl group; R^1 is a methyl group; R^2 is an ethyl group, a cyclopropylmethyl group, an allyl group or a propargyl group; X^1 is a hydrogen atom; X^2 is a halogen atom or a methylthio group each bonded at the 2-position of the benzene ring; and X^3 is an isopropyl group or a dimethylamino group each bonded at the 4-position of the benzene ring.

3. A tetrahydropyridylpyrimidine derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein, in formula (I), Ar is at the 5-position of the tetrahydropyridine ring and is a phenyl group substituted with 1 to 3 substituents selected from a halogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms and a trifluoromethyl group, a phenyl group, a thienyl group or a furanyl group; R^1 is a methyl group; R^2 is an ethyl group, a cyclopropylmethyl group, an allyl group or a propargyl group; X^1 is a hydrogen atom; x^2 is a halogen atom or a methylthio group each bonded at the 2-position of the benzene ring; and X^3 is an isopropyl group or a dimethylamino group each bonded at the 4-position of the benzene ring.

4. A 4-tetrahydropyridylpyrimidine derivative or a pharmaceutically acceptable salt thereof according to claim 2, wherein Ar is a phenyl group substituted with a halogen atom.

5. A 4-tetrahydropyridylpyrimidine derivative or a pharmaceutically acceptable salt thereof according to claim 3, wherein Ar is a phenyl group substituted with an alkyl group having 1 to 5 carbon atoms.

6. A CRF receptor antagonist containing the 4-tetrahydropyridylpyrimidine derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5 as an active ingredient.

7. Use of the 4-tetrahydropyridylpyrimidine derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5 as a CRF receptor antagonist.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/01330

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 7-509725, A (Pfizer Inc.), October 26, 1995 (26. 10. 95), Claims & WO, 94/13643, A1 & FI, 9305674, A & AU, 9454548, A & TW, 238303, A & ZA, 9309404, A & NO, 9502395, A & EP, 674624, A1 & CZ, 9501585, A & NZ, 257770, A & CN, 1092768, A & US, 5712303, A	1-6

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